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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/070,882	03/11/2002	Richard William Titball	41577/270459	2737

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EXAMINER	
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ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/070,882	TITBALL ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,23 and 25-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 23 and 25-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

REQUEST FOR CONTINUED EXAMINATION

1) A request for continued examination under 37 C.F.R 1.114, including the fee set forth in 37 C.F.R 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R 1.114, and the fee set forth in 37 C.F.R 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 C.F.R 1.114. Applicants' submission filed on 02/08/07 has been entered.

Applicants' Amendment

2) Acknowledgment is made of Applicants' amendment filed 02/08/07 in response to the final Office Action mailed 08/08/06.

Status of Claims

3) Claims 1, 23, 25, 26 and 28-31 have been amended via the amendment filed 02/08/07.

Claims 24 has been canceled via the amendment filed 02/08/07.

Claims 1, 23 and 25-32 are pending and are under examination.

Prior Citation of Title 35 Sections

4) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

5) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Objection(s) Withdrawn

6) The objection to the specification made in paragraph 3(A)(a) of the Office Action mailed 02/23/06 and maintained in paragraph 3 of the Office Action mailed 08/08/06, is withdrawn in light of Applicants' amendment to the specification.

7) The objection to the specification made in paragraph 4 of the Office Action mailed 08/08/06 is withdrawn in light of Applicants' amendment to the specification.

Rejection(s) Moot

8) The rejection of claims 24 made in paragraph 22 of the Office Action mailed 08/08/06

under 35 U.S.C § 112, first paragraph, as containing new subject matter, is moot in light of Applicants' cancellation of the claim.

9) The rejection of claim 24 made in paragraph 23(c) and 23(f) of the Office Action mailed 08/08/06 under 35 U.S.C § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claim.

Rejection(s) Withdrawn

10) The rejection of claims 1, 23 and those dependent therefrom and from claim 24 made in paragraph 22 of the Office Action mailed 08/08/06 under 35 U.S.C § 112, first paragraph, as containing new subject matter, is withdrawn in light of Applicants' amendments to the claims.

11) The rejection of claim 1 made in paragraph 23(a) of the Office Action mailed 08/08/06 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

12) The rejection of claims 23 and 1 made in paragraph 23(b) of the Office Action mailed 08/08/06 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.

13) The rejection of claim 29 made in paragraph 23(d) of the Office Action mailed 08/08/06 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

14) The rejection of claims 31 and 32 made in paragraph 23(e) of the Office Action mailed 08/08/06 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.

15) The rejection of claims 23 and 25-32 made in paragraph 23(f) of the Office Action mailed 08/08/06 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the base claim.

Rejection(s) under 35 U.S.C § 112, First Paragraph (New Matter)

16) Claims 1 and those dependent therefrom are rejected under 35 U.S.C § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the

application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 1, as amended, is drawn to a method of enhancing expression of a desired protein at mucosal effector sites 'of a mammal, the' method comprising placing a nucleotide sequence encoding the protein to be expressed under control of a promoter having the nucleotide sequence of SEQ ID NO: 2 'in a recombinant gut-colonizing microorganism, administering the microorganism to the mammal, and causing expression of the desired protein in mucosal cells'. The currently claimed method of 'enhancing expression of a desired protein at mucosal effector sites of a mammal' includes the steps of: (a) placing a nucleotide sequence encoding the protein to be expressed under control of a promoter having the nucleotide sequence of SEQ ID NO: 2 in a recombinant gut-colonizing microorganism; (b) administering the microorganism to the mammal; and (c) causing expression of the desired protein in mucosal cells. As recited currently, the mucosal cells are not required to be from the mammal to whom the recombinant gut-colonizing microorganism is administered. Applicants state that support for the claim amendments can be found at lines 22-28 and 30-31 of page 4 of the instant application. However, the description in these parts of the specification is limited to a recombinant gut-colonizing microorganism comprising the P_{phop} promoter 'being operatively interconnected with a nucleic acid which encodes a heterologous protein', which is able to induce a protective immune response 'against a different organism', but is not supportive of a method as claimed which encompasses expression of a homologous protein within the scope of the claims wherein the promoter is not required to be operatively interconnected with a nucleic acid which encodes the homologous protein. Lines 19 and 20 of page 4 of the specification specifically recite that the construct containing the P_{phop} promoter 'contains no further elements of the .... phoP .. gene'. Therefore, these parts of the specification support --placing a nucleotide sequence encoding a heterologous protein under the control of a promoter consisting of SEQ ID NO: 2, said promoter being operatively interconnected to the nucleotide sequence--. Lines 22-31 on page 4 of the specification describe one embodiment of the invention that describes the product, a recombinant gut-colonizing microorganism, but does not describe a method as claimed in the instant claims. Lines 6-11 on page 4 of the specification describe a method that does not use a recombinant gut-colonizing microorganism and its administration to a mammal. Therefore, the currently claimed method constitutes new matter. *In*

re Rasmussen, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after 608.04(c).

Applicants are invited to point to specific line and page numbers of the specification, as originally filed, that provide descriptive support for the limitations identified above, or alternatively, remove the new matter from the claim. Applicants should specifically point out the support for any amendment made to the disclosure. See MPEP 714.02 and 2163.06.

Rejection(s) under 35 U.S.C § 112, First Paragraph (Scope of Enablement)

17) Claims 1, 23 and 25-32 are rejected under 35 U.S.C § 112, first paragraph, because the specification, while being enabling for a method of inducing a serum or mucosal antibody response against F1 antigen of *Yersinia pestis* in a mammal comprising orally administering to said mammal a dosage of an attenuated recombinant *Salmonella* spp. expressing said F1 antigen wherein said *Salmonella* spp. comprises the nucleotide sequence encoding said F1 antigen under the control of a promoter consisting of the nucleotide sequence of SEQ ID NO: 2, said promoter being operatively interconnected to the nucleotide sequence, does not reasonably provide enablement for a method of enhancing expression of any desired protein at mucosal effector sites of a mammal, said method comprising placing a nucleotide sequence encoding the protein to be expressed under control of a promoter having the nucleotide sequence of SEQ ID NO: 2 in a generic recombinant gut-colonizing microorganism, administering the microorganism to the mammal by any generic route, and causing expression of the desired protein in mucosal cells, as claimed broadly. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to reproducibly make and use the full scope of the invention as claimed.

Instant claims are evaluated based on the *Wands* analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability of the art; and
- The breadth of the claims.

The nature of the invention in the instant application is about enhancing expression of any desired protein at mucosal effector sites of a mammal said method comprising placing a nucleotide sequence encoding the protein to be expressed under control of a promoter having the nucleotide sequence of SEQ ID NO: 2 in any generic recombinant gut-colonizing microorganism, administering the microorganism to the mammal by any generic route, and causing expression of the desired protein in mucosal cells. Because of the open claim language 'having', the limitation 'having the nucleotide sequence of SEQ ID NO: 2' encompasses SEQ ID NO: 2 comprising any other nucleotide bases on one or both sides of SEQ ID NO: 2. The method of claim 23 and claims dependent therefrom is required to induce 'a protective immune response' against a generically recited 'pathogen', including *Yersinia pestis*. The limitation 'gut-colonizing microorganism' encompasses gut-colonizing pathogenic and non-pathogenic microorganisms, aerobic and anaerobic bacteria, fungi, parasites, and viruses. The limitation 'gut-colonizing microorganism' encompasses highly virulent or invasive bacteria, fungi, parasites etc. having the ability to cause fatal infections in a mammal upon administration. The gut-colonizing pathogenic and non-pathogenic bacteria include various species of *Salmonella*, *Shigella*, *Vibrio*, *Escherichia*, *Lactobacillus*, *Lactococcus*, *Bifidobacterium*, *Bacteroides*, *Clostridium*, *Fusobacterium*, *Peptostreptococcus*, *Ruminococcus*, *Eubacterium*, *Peptococcus*, *Streptococcus agalactiae* etc. The gut-colonizing pathogenic and non-pathogenic fungi include species of *Candida*, *Aspergillus*, *Saccharomyces*, *Penicillium* etc. The gut-colonizing parasites include *Giardia*, *Cryptosporidium*, *Ascaris*, *Taenia*, *Entamoeba*, *Stringyloides*, *Trichuris*, *Hymenolepis*, *Enterobius* etc. The gut-colonizing viruses include Enteroviruses, Rotavirus, bacteriophages, enteric Adenovirus, Norwalk virus, Astrovirus, Calicivirus, Hepatitis E virus, Torovirus, Coronavirus etc. The step of 'administering' the recombinant gut-colonizing microorganism encompasses administration via non-oral routes that do not effect colonization of the gut, for example, intramuscular, intradermal, transcutaneous, intrathecal, subcutaneous routes etc. The limitation 'gut-colonizing microorganism' in claim 1 is not required to be attenuated, but can be infectious or virulent. However, the last paragraph of page 6 of the specification emphasizes the importance of 'suitably attenuating' recombinant gut-colonizing microorganisms of the instant invention 'so that the host does not experience significant harmful effects as a result of infection by the microorganism', indicating the necessity or requirement for the recited

gut-colonizing microorganism to be --attenuated--. The method as claimed, which includes administering a non-attenuated gut-colonizing microorganism is not enabled.

In order to enhance expression of a desired protein at mucosal effector sites of a mammal, the stable maintenance of the promoter-nucleotide sequence-containing plasmid in the recombinant gut-colonizing bacteria *in vivo* is critical so that the administered recombinant bacteria expressing the heterologous protein are able to colonize the targeted tissues *in vivo*. See last paragraph on page 217 of Leary *et al.* (*Contrib. Microbiol. Immunol.* 13: 216-217, 1995). The description in the first full paragraph on page 10 of the instant specification indicates that it is very important for the recited gut-colonizing microorganism comprising the nucleotide sequence encoding the protein under the control of the recited promoter to have the ability to effect invasion in the host. This part of the specification documents variability in the ability to invade the host based on the promoters carried in a given gut-colonizing microorganism. The state of the art at the time of the instant invention recognized that although several constructs capable of transforming gut dwelling organisms such as *S. typhimurium* and *S. typhi* such that they produce *Yersinia pestis* F1 antigen have been identified, most of these affect the organism such that *it can no longer function effectively in the gut*, at least in so far as *it cannot express the antigen, i.e., being unstable and losing plasmid.* See abstract of Titball *et al.* (WO 95/18231). Thus, the state of the art documents unpredictability with regard to the ability of even a specific recombinant gut-colonizing bacterium species, let alone a generic recombinant gut-colonizing microorganism, to stably and successfully express a heterologous protein and invade the host cells. Other than an attenuated *S. typhimurium* or attenuated *S. typhi* expressing the F1 antigen of *Y. pestis* under the control of a promoter consisting of the nucleotide sequence of SEQ ID NO: 2, the instant specification does not enable any generic recombinant gut-colonizing microorganism, stably and successfully expressing a heterologous protein under the control of a promoter having the nucleotide sequence of SEQ ID NO: 2 and capable of invading the cells of a mammal upon oral or non-oral administration of the same to a mammal such that it induces a 'protective immune response' in the mammal against any generic 'pathogen'. One of the pathogens to which a 'protective immune response' is induced in a mammal to which the recited gut-colonizing recombinant microorganism is administered, is *Yersinia pestis*. See claim 29. The mammal to whom the recited gut-colonizing recombinant microorganism is administered is

a human. The 'administration' encompasses parenteral administration. However, the state of the art indicates lack of evidence for protection against plague via parenteral immunization. For instance, Glynn *et al.* (*Vaccine* 23: 1957-1965, 2005) teach the following (see first full paragraph in left column on page 1963) [Emphasis added]:

> There is **no evidence to indicate that parenteral immunization will be effective in preventing plague in humans following aerosol exposure**. *Y. pestis* causes primary pneumonia in the lungs subsequent to aerosol exposure (in contrast to inhalation anthrax which starts as a systemic disease) and mice may not be the best model to demonstrate whether mucosal immunity will contribute to protection.

The instant application demonstrates that *Salmonella* expressing P_{phop}-F1 induces mucosal antibody responses to the F1-antigen in both the gut and the lungs, and serum antibody response in mice that were *orally* or intragastrically administered with 10^9 CFU of the recombinant *S. typhimurium* SL3261 comprising the P_{phop}-F1 plasmid. See the paragraph bridging pages 11 and 12; Examples 3-6; and Figures 3-5. There is no evidence that the mice administered with 10^9 CFU of the recombinant *S. typhimurium* SL3261 comprising the P_{phop}-F1 plasmid were challenge- infected with an F1-containing or F1-negative virulent strain of *Y. pestis.* This is critically important considering what is known in the state of the art on protection against plague. The state of the art teaches that F1 antigen of *Y. pestis* is not the only virulence factor and protective antigen, and that F1 antigen alone does **not** protect against naturally occurring and genetically mutated F1-negative strains. For instance, Leary *et al.* (*Microb. Pathogen.* 23: 167-179, 1997) taught the following (see page 168) [Emphasis added]:

> The precise contribution of many of the virulence determinants to the pathogenesis of plague is **not fully understood**, and as a result, *it is difficult to predict the immunogenic potential of candidate vaccines.*
>
> ..... it has been shown that mice vaccinated with F1 antigen alone were **not** protected against naturally occurring or genetically mutated F1-negative strains .... These mutant strains retain their virulence in mice ... and African green monkeys ... Thus, *to provide effective protection against plague, it is desirable that F1 antigen should be administered with other antigens.*

Therefore, the enabling disclosure in the instant specification is limited to a method of inducing a serum or mucosal antibody response against F1 antigen of *Yersinia pestis* in a mammal comprising orally administering to said mammal a dosage of an attenuated recombinant *Salmonella* spp. expressing said F1 antigen wherein said *Salmonella* spp. comprises the nucleotide sequence encoding said F1 antigen under the control of a promoter consisting of the nucleotide sequence of SEQ ID NO: 2, said promoter being operatively interconnected to the nucleotide sequence. However, beyond this scope, the specification is not enabling for a method

of enhancing expression of any desired protein at mucosal effector sites of any mammal, said method comprising placing a nucleotide sequence encoding the protein to be expressed under control of a promoter having the nucleotide sequence of SEQ ID NO: 2 in any generic recombinant gut-colonizing microorganism, administering the microorganism to the mammal by any generic route, and causing expression of the desired protein in mucosal cells, as claimed broadly. A considerable amount of undue experimentation would have been required by one of ordinary skill in the art at the time of the effective filing date of the instant application to reproducibly practice the invention as claimed, due to the lack of specific guidance and direction, the lack of disclosure enabling the full scope, the art-recognized unpredictability in the pertinent art, the breadth of the claims, and the quantity of experimentation necessary. The claims are viewed as not meeting the scope of enablement provisions of 35 U.S.C § 112, first paragraph.

Rejection(s) under 35 U.S.C § 112, Second Paragraph

18) Claims 1, 23 and 25-32 are rejected under 35 U.S.C § 112, second paragraph, as being indefinite, for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claim 1 is vague, confusing, indefinite, and internally inconsistent in the limitation: 'enhancing expression of a desired protein at mucosal effector sites of a mammal ..... and causing expression of the desired protein in mucosal cells', because it is unclear how a 'method of enhancing expression of a desired protein at mucosal effector sites of a mammal' can have the ultimate step or result of 'causing expression of the desired protein in mucosal cells'. Is the scope of 'enhancing expression of a desired protein at mucosal effector sites of a mammal' the same as the scope of 'causing expression of the desired protein in mucosal cells'?

(b) Claim 1 is vague and indefinite in the limitation: 'causing expression of the desired protein in mucosal cells' without distinctly pointing out where the desired protein is expressed. Is the desired protein expressed *in vivo* in mucosal cells of the mammal that is administered with the recombinant gut-colonizing microorganism, or is it expressed *in vitro* or *ex vivo* in mucosal cells obtained from the mammal that is administered with the recombinant gut-colonizing microorganism? Clarification/correction is requested.

(c) Claim 1 is vague, indefinite and has improper antecedent basis in the limitation: 'the protein to be expressed under control' (see line 3). The limitation in the earlier part of the

claim recited 'a desired protein' (see lines 1 and 2). For the purpose of distinctly claiming the subject matter, it is suggested that Applicants replace the above-identified limitation with the limitation --the protein under the control--.

(d) Claims 23 and 25-32, which depend directly or indirectly from claim 1, are also rejected as being indefinite because of the indefiniteness identified above in the base claim.

Remarks

19) Claims 1, 23 and 25-32 stand rejected.

20) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. The Fax number for submission of amendments, responses and/or papers is (571) 273-8300, which receives transmissions 24 hours a day and 7 days a week.

21) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

22) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Jeffrey Siew, can be reached on (571) 272-0787.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

S. DEVI, PH.D.
PRIMARY EXAMINER

April, 2007